AMENDMENTS TO THE SPECIFICATION

On page 1, lines 1-2, please replace the title with the following amended title:
-- Anti-idotype Anti-CEA Antibody Molecules and ~~its Use as a Cancer Vaccine~~ Methods --

On page 1, before the heading "FIELD OF THE INVENTION" at line 4, please add the following paragraph:

-- This application is the National Stage of International Application No. PCT/EP03/03580 filed on April 7, 2003. --

Please replace the paragraph beginning at line 17 on page 4 of the specification with the following amended paragraph:

-- The invention provides modified polypeptides wherein the polypeptide sequences are derived in large part from the murine anti-idiotype antibody 708. Where the polypeptide sequences share sequence tracts in common with the V-regions of antibody 708 (SEQ ID NO: 1 and 2) there are provided a number of embodiments in which sequence tracts from either CEA (SEQ ID NO: 3) and / or the CD55 antigen (SEQ ID NO: 4) are additionally provided. In a further embodiment there are provided polypeptide sequences in which amino acid substitutions have been conducted to result in the removal of undesired T-cell epitopes. In such compositions the intent is to focus the induced immune response to the CEA and / or CD55 epitope component and remove competing peptide epitopes not contributing to the desired anti-cancer response. --

Please replace the paragraph beginning at line 4 on page 5 of the specification with the following amended paragraph:

-- The variable region sequences of the 708 antibody (SEQ ID NO: 1 and SEQ ID NO: 2) have been obtained and analyzed for the presence of sequence elements homologous to regions of the

CEA protein. The first and second complementarity determining regions of the H-chain (CDRH2 (SEQ ID NO: 5) and CDRH3 (SEQ ID NO: 6) show homology with CEA (SEQ ID NO: 3) but not to the closely related molecules NCA or BGP. The 708 variable region and the complementarity determining regions (CDRs) of the H-chain (SEQ ID NO: 1) in particular represent a molecular mimic of particular elements of the CEA molecule and are likely to provide the basis for the idotypic nature of the 708 antibody for CEA. --

Please replace the paragraph beginning at line 13 on page 5 of the specification with the following amended paragraph:

-- The present invention comprises modified derivative versions of the parental antibody 708. In all preferred embodiments the modified 708 molecules include a human C-region domain in place of the parental murine C-regions. Other modifications are conducted in the V-region domains of the molecule. Such modifications can be summarised as comprising one or more changes directed towards the following objectives, wherein at least ~~on~~ one change directed to a CEA sequence has to be involved:

I. Conversion of regions of existing CEA homology into regions CEA sequence identity.
II. Replacement of existing short sequence tracts with tracts of CEA derived sequence.
III. Replacement of existing short sequence tracts with tracts of antibody 107AD5 derived sequence.
IV. Replacement of existing short sequence tracts with tracts of CD55 derived sequence.
V. Removal of undesired T-cell epitopes by replacement of specific amino acid residues with alternative amino acid residues. --

Please replace the paragraph at lines 1-6 on page 7 of the specification with the following amended paragraph:

-- A corresponding immunoglobulin molecule comprising within the variable regions additionally CEA derived sequence tracts which are MHC class I epitopes responding to CEA positive human cancer cells, preferably TLLSVTRNDV (SEQ ID NO: 7) and YLSGANLNL

(SEQ ID NO: 8), wherein in a preferred embodiment of the invention said sequences are part of or form completely one ore more of the CDRs of the light chain of said immunoglobulin. --

Please replace the paragraph at lines 15-22 on page 7 of the specification with the following amended paragraph:

-- A corresponding immunoglobulin molecule, wherein the variable heavy and / or light chain comprises one or more sequence tracts in identity with the sequence tracts selected from the group:

(i) 345-354 of ~~human CEA~~ SEQ ID NO: 3 (human CEA);

(ii) 387-396 of ~~human CEA~~ SEQ ID NO: 3 (human CEA);

(iii) 571-579 of ~~human CEA~~ SEQ ID NO: 3 (human CEA);

(iv) 629-645 of ~~human CEA~~ SEQ ID NO: 3 (human CEA);

(v) 148-167 of ~~human CD55~~ SEQ ID NO: 4 (human CD55). --

Please replace the paragraph at lines 11-19 on page 9 of the specification with the following amended paragraph:

-- Under the scheme of the present invention there are provided 4 different H-chain V-region sequences (SEQ ID NO: 9-12) and 2 different L-chain V-region sequences (SEQ ID NO: 13-14). The present disclosure provides no limit to the possible combinations of H-chain and L-chain that may be provided to constitute a complete antibody molecule. Constitution of the complete antibody molecule may be achieved by recombinant DNA techniques and methods for purifying and manipulating antibody molecules well known in the art. Polynucleotide (e.g. DNA) molecules encoding the polypeptide sequences disclosed herein are equally considered under the scope of the present and are preferred embodiments. --

Please replace the paragraph beginning at line 14 on page 10 of the specification with the following amended paragraph:

-- **Figure 3** shows the protein sequence (single letter code) of the variable regions of antibody 708. Panel A = heavy chain (SEQ ID NO: 1); Panel B= light chain(SEQ ID NO: 2). Underlined sequences are CDRs. FR = framework sequence. CDR designations are according to the scheme of Kabat [Martin, A.C.R. (1996), ~~*PROTEINS: Structure, Function and Genetics*, 25 130-133~~ *PROTEINS: Structure, Function and Genetics*, 25 130-133] but residue numbering has been modified individually according to this invention. --

Please replace the paragraph beginning at line 21 on page 10 of the specification with the following amended paragraph:

-- **Figure 4** shows the protein sequence (single letter code; SEQ ID NO: 9) of 708VH1. This sequence comprises 708VH, with un-desired epitopes removed. Underlined sequences are CDRs. --

Please replace the paragraph beginning at line 25 on page 10 of the specification with the following amended paragraph:

-- **Figure 5** shows the protein sequence (single letter code; SEQ ID NO: 10) of 708VH2. This sequence comprises 708VH, with un-desired epitopes removed and incorporating additional CEA related sequences. Underlined sequences are CDRs. --

Please replace the paragraph beginning at line 29 on page 10 of the specification with the following amended paragraph:

-- **Figure 6** shows the protein sequence (single letter code; SEQ ID NO: 11) of 708VH3. This sequence comprises 708VH, with un-desired epitopes removed and incorporating additional CEA and CD55 derived sequences. Underlined sequences are CDRs. --

Please replace the paragraph beginning at line 33 on page 10 and continuing through line 2 on page 11 of the specification with the following amended paragraph:

-- **Figure 7** shows the protein sequence (single letter code; SEQ ID NO: 12) of 708VH4. This sequence comprises 708VH, with un-desired epitopes removed and incorporating additional CEA and 105AD7 derived sequences. Underlined sequences are CDRs. --

Please replace the paragraph beginning at line 4 on page 11 of the specification with the following amended paragraph:

-- **Figure 8** shows the protein sequence (single letter code; SEQ ID NO: 13) of 708VL1. This sequence comprises 708VL, with un-desired epitopes removed. Underlined sequences are CDRs. --

Please replace the paragraph beginning at line 8 on page 11 of the specification with the following amended paragraph:

-- **Figure 9** shows the protein sequence (single letter code; SEQ ID NO: 14) of 708VL2. This sequence comprises 708VL, with un-desired epitopes removed and incorporating additional CEA related sequences. Underlined sequences are CDRs. --

Please replace the paragraph beginning at line 12 on page 11 of the specification with the following amended paragraph:

-- **Figure 10** shows the protein sequence (single letter code; SEQ ID NO: 3) of CEA. --

Please replace the paragraph beginning at line 14 on page 11 of the specification with the following amended paragraph:

-- **Figure 11** shows protein sequence (single letter code; SEQ ID NO: 4) of CD55 antigen. --

Please replace the paragraph beginning at line 16 on page 12 and continuing through line 2 on page 13 of the specification with the following amended paragraph:

-- Where the first modification of the 708 antibody is conversion to a chimaeric antibody and therefore involved engineering of the constant region, subsequent modifications, and hence embodiments of the invention, are directed towards engineering of the V-regions of the parental 708 antibody (SEQ ID NO: 1 and 2). The V-region sequences of 708 have been described previously [WO98/52976] and the protein sequences are again provided herein as Figure 3. The complementarity determining region (CDR) sequences have been analyzed for regions of homology with CEA and related sequences such as NCA. The CDRH2 (SEQ ID NO: 5) shows homology with three specific regions of CEA (SEQ ID NO: 15, 17 and 18) and two of these also share homology with NCA. A third region is in an area specific to CEA. As the original Ab1 NCRC23, bound to a CEA specific region it is not unexpected to find that the anti-idiotype 708 should contain CEA-homlogous sequence. In addition to the region found in CDRH2, the CDRH3 (SEQ ID NO: 6) showed homology with three regions of CEA (SEQ ID NO: 19, 20, 22), and these also share homology with NCA. Comparative analysis of polypeptide and polynucleotide sequences is well known in the art and a number of software tools enable these procedures. One such software tool, as used for the comparison of the antibody 708 and CEA sequences as described above, is "DNAstar", (DNASTAR Inc, Madison, WI, USA) which has implementations of several alignment algorithms including Lipman & Pearson [Lipman & Pearson (1985), ~~*Science* 227:1435-1441~~ *Science* 227:1435-1441] which is particularly useful for protein sequence similarities. --

Please replace the paragraph beginning at line 7 on page 14 of the specification with the following amended paragraph:

-- The polypeptide molecules of the present are designed with the purpose of providing immunogenic epitopes to the immune system of the subject patient such that the patients immune system becomes re-directed to eliminate cells expressing CEA. It is important therefore to evoke

humoral and cellular arms of the immune system and this is provided by delivery of both potent T-helper epitopes and MHC class I restricted epitopes. A number of MHC class I restricted epitopes have been identified previously within the CEA sequence and in some instances have been the subject of clinical trial [Kwong, Y. et al (1995) *JNCI* 87: 982-990]. In the present invention, CEA derived sequence tracts TLLSVTRNDV (SEQ ID NO: 7, residues 345-353 of SEQ ID NO: 3) and YLSGANLNL (SEQ ID NO: 8, residues 571-579 of SEQ ID NO: 3) which are known MHC class I epitopes have been engineered into the CDRs of the light chain. --

Please replace the paragraph at lines 15-28 on page 15 and continuing through line 4 on page 27 of the specification with the following amended paragraph:

-- Accordingly the invention provides modified V-region sequences containing tracts of sequence which share identity to regions of the CEA molecule. The invention also discloses V-region sequences that share identity with tracts of sequence present in the CD55 molecule. In a further embodiment still, there is disclosed a V-region sequence modified to contain a sequence tract from the antibody 107AD5. Specifically there are provided V-region sequences containing residues in identity with residues 345-354, 386-397, 571-579 and 629-645 from the CEA sequence (SEQ ID NO: 3); and sequences in identity with residues 148-167 of the CD55 molecule (SEQ ID NO: 4). A sequence corresponding to the majority of framework 1 of the VH chain of antibody 107AD5 is incorporated within one disclosed variant of the present invention. Specifically a composition according to the sequence of Figure 7 (SEQ ID NO: 12) is preferred and contains sequence elements of the 107AD5 VH framework 1 region in replacement of the corresponding region within the 708VH3 sequence described herein. --

Please replace the paragraph beginning at line 30 on page 15 and continuing through line 7 on page 16 of the specification with the following amended paragraph:

-- It will be appreciated that for the CEA sequence elements inserted into the VH chains of the modified 708 molecule, the insertions have been into regions where significant homology to the CEA sequence existed in the parent molecule. Thus a preferred VH composition as shown in

Figure 5 (SEQ ID NO: 10) comprises CEA residues 629-645 (of SEQ ID NO: 3) inserted into the VH chain at a zone encompassing the CDRH2 region, and also includes CEA residues 386-397 of SEQ ID NO: 3 inserted into the VH chain at a zone encompassing the CDRH3 region. A preferred VL chain composition provides CEA sequence elements 345-354 and 571-579 of SEQ ID NO: 3 inserted into the VL chain at regions encompassing the CDRL1 and CDRL3 zones respectively (Figure 9; SEQ ID NO: 14). A preferred composition containing CD55 sequence elements such as region 148-167 contains the said CD55 sequence inserted into a VH chain within a zone comprising the distal part of framework 1 and the entirety of CDRH1 (Figure 6; SEQ ID NO: 11). --